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Mark T. Garrett

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#21

In re Application of:
Zhang et al.

Serial No.: 09/413,109

Filed: October 6, 1999

For: METHODS FOR THE ADMINISTRATION OF ADENOVIRUS p53 (AS AMENDED)

Group Art Unit: 1636

Examiner: Guzo, D.

Atty. Dkt. No.: INRP:087/GNS

RESPONSE TO OFFICE ACTION
DATED AUGUST 29, 2001

Commissioner for Patents
Washington, D.C. 20231

Commissioner:

This paper is submitted in response to the Office Action dated August 29, 2001 for which the three-month date for response was November 29, 2001.

A request for a three-month extension of time to respond is included herewith along with the required fee. This three-month extension will bring the due date to February 28, 2002, which is within the six-month statutory period. Should such request or fee be deficient or absent, consider this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10012509/GNS.

Reconsideration of the application is respectfully requested.

RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 22-97 were pending prior to the Office Action dated August 29, 2001. For the Examiner's convenience, the pending claims are attached hereto as Appendix A.

B. Claims 79-97 Are Enabled

The Action rejects claims 79-97 under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably enable treating any cancer with an adenovirus comprising the p53 gene. The Action alleges gene therapy is extremely unpredictable and cites the references of Fox, Kmiec, Anderson, Verma, Anderson, and Ross as support for this contention. It further cites the reference of Gomez-Navarro, which is said to note that current vectors are not suitable for intravenous or other systemic methods of delivery to cancers for treatment. The Action concludes that the skilled artisan would have had to conduct undue and excessive experimentation in order to practice the claimed invention. Applicants respectfully traverse this rejection.

1. The specification provides ample direction to practice the claimed invention

"The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" MPEP 2164.08 (citing *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q. 1510, 1513 (Fed. Cir. 1993)). With respect to this rejection, the claimed invention is generally directed to "A method of treating a human cancer patient having a tumor, comprising administering by direct injection of the tumor an amount of an adenovirus composition effective to inhibit growth of tumor cells, wherein said adenovirus composition comprises an adenovirus vector construct comprising a p53 gene, dispersed in a

pharmacologically acceptable solution." Claim 79. As argued previously, Applicants note that the specification teaches how to make an "adenovirus composition compris[ing] an adenovirus vector construct comprising a p53 gene," at Examples 1-3, it shows that tumor cells are suppressed in *in vitro* and *ex vivo* studies, at Examples 4 and 5, and finally, it shows that treatment can be effected *in vivo* after intratracheal administration of Ad-p53 to mice with tumors, at Example 6. Furthermore, the specification indicates in Example 7 that direct administration is "suitable for p53 adenovirus treatment methods." It would not require undue experimentation to practice "direct administration" based on the example of intratracheal administration in the specification.

Applicants respectfully note that "it is incumbent upon the Patent Office...to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.05 (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971)). As will be discussed below, none of the references cited in the Action cast doubt as to the sufficiency of the present disclosure to allow a person of ordinary skill in the art to practice the invention without undue experimentation. There is no reason provided why a person could not take the disclosure and practice the invention as claimed in claims 79-97. Accordingly, the specification teaches how to make and use the claimed invention, and thus, it enables claims 79-97.

2. Contentions of unpredictability are undocumented

The Action argues that gene therapy is extremely unpredictable. It says, "Indeed, given the vast variety of oncogenes, tumor suppressor genes and other genetic phenomena involved in tumorigenesis, it is totally unpredictable whether the instant adenoviral vector can prevent

growth of human cancer cells which are the result of mutations in tumor suppressor genes unrelated to p53 or the result of activation of oncogenes, etc." Page 3. The Action also contends it is not clear that the instant vectors can prevent growth of cancer cells that have a normal p53 gene. *Id.* Applicants point out that the PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-370 (CCPA. 1971). With respect to those specific contentions, the Action provides no such evidence to challenge the specification's assertion that a method of treatment would be effected. The specification indicates that tumor cells may be treated, and the claims do not limit tumor cells to those lacking p53. This must be taken at face value unless the Action can point to evidence that undermines this assertion.

Moreover, there are references that indicate the invention will work as claimed; these references indicate that tumor cells carrying a wild-type p53 gene are susceptible to p53 gene therapy. For example, the reference of Hamada *et al.* (Appendix B) shows that a number of p53-positive cervical cell lines —HeLa, C4-I, MS751, ME180, CaSki, and SiHa—are amenable to p53 gene therapy using adenovirus. This reference addresses the issue of whether cancers with mutations unrelated to p53 can be treated by the claimed invention. Thus, contrary to the Action's unsupported assertion, there is no reason to doubt the invention will work as claimed.

3. The references cited in the Action are irrelevant

The Action urges that Applicants review the references of Fox, Kmiec, Anderson, Verma *et al.*, and Ross to show that gene therapy is generally unpredictable. Applicants point out that in the Response to Office Action dated September 8, 2000, they indicated why each of these references was inapplicable to the invention claimed in this application. Without repeating the

content of that response, Applicants emphasize that those references do not address **p53** gene therapy as recited in the claims, and instead, generalize about gene therapy. Furthermore, none of these articles state that gene therapy will not work and is a complete failure. Instead, they focus on more clinical issues, which are above and beyond the standards for patentability. *See In re Krimmel*, 292 F.2d 948, 954 (C.C.P.A. 1961) ("There is nothing in the patent statute or any other statutes . . .which gives the Patent Office the right or the duty to require an applicant to prove that compounds or other materials which he is claiming, and which he has stated are useful for 'pharmaceutical applications,' are safe, effective, and reliable for use with humans.").

As for the cited reference of Gomez-Navarro, it too fails to address p53 gene therapy, much less the methods of the claimed invention. It does not say that the invention described and claimed in the specification will not work. Moreover, it is not clear that what the Action calls "obstacles" discussed in the Gomez-Navarro reference apply to claims 72-97. The Action contends that the obstacles involve "the remarkably heterogeneous nature of the patterns of expression of relevant oncogenes in many human tumors, the fact that some mutated genes exhibit a transdominant effect which cannot be overcome by merely supplying the wild-type gene, the poor level of understanding of the tumor-supportive micro-environment and of multicellular tumor phenomena which can overcome any therapeutic effect of the vector, etc." Action at page 4. Applicants note that there is no reason to believe that these obstacles pertain specifically to the claimed invention, particularly because the specification shows that supplying the wild-type gene **does** effect tumor suppression and that tumor suppression was observed regardless of an understanding of the tumor-supportive micro-environment. The working examples in the specification rebut these concerns with respect to p53 gene therapy, and thus, these concerns have no applicability to the claimed invention. Furthermore, the sentence quoted

by the Action that gene therapies have been restricted to treatment of compartmentalized tumors, at page 877, only strengthens the argument that claims 79-97—which recite direct injection—are enabled.

Like the other articles about gene therapy that are cited in the Action, the Gomez-Navarro reference focuses on a standard for clinical applications that is inappropriate for evaluating patentability. For patentability, proof of efficacy in clinical trials involving humans is not a requirement for patentability. *See In re Brana,* 51 F.3d 1560 (Fed. Cir. 1995). Additionally, even this reference, which focuses on problems with gene therapy, ultimately concludes, "[I]t is anticipated that these promising results observed in pre-clinical studies will translate quickly into the clinic for amelioration of life-threatening malignant diseases." Gomez-Navarro at 881. Thus, Gomez-Navarro does not ultimately stand for the proposition that gene therapy will not work generally, much less work as taught in the specification of this application.

Furthermore, with respect to the applicability of this reference to the invention claimed in claims 79-97, there are scientific articles that indicate direct injection into a tumor will work, which rebuts the contention of the Gomez-Navarro reference. For example, the reference of Clayman *et al.* (Appendix C) shows that intratumoral injection of Ad-p53 caused tumor regression in patients with head and neck cancer. The Clayman reference disproves any assertion that the Gomez-Navarro reference is evidence that direct injection of Ad-p53 will not work as taught by the specification. Thus, there is no reason to doubt the invention is adequately enabled by the specification.

C. Claims 22-78 Are Enabled

The Action rejects claims 22-78 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. It indicates the same grounds of

rejection for claims 79-97 apply to claims 22-78. It further notes that Gomez-Navarro indicates that *in vivo* cancer gene therapy strategies involve direct administration of the vectors to compartmentalized tumors and that present vectors are inadequate for delivery intravenously or by other systemic methods. Applicants respectfully traverse this rejection.

Applicants assert that the previous arguments with respect to the rejection of claims 79-97 applies to the rejection of claims 22-78 (to the extent that the rejection of claims 22-78 is similarly grounded in the rejection of claims 79-97). The specification provides a teaching that allows a person of ordinary skill in the art to practice the invention without undue experimentation, and none of the references cited by the Action provide evidence that the invention will not work as described and claimed.

Applicants further note that there are other scientific articles that rebut any contention that intravenous or systemic delivery of adenovirus vectors will not work. The article of Nemunaitis *et al.* (Appendix D) indicates that "intravenous administration of genetically altered adenovirus is a feasible approach." In Nemunaitis *et al.*, the authors report their findings from a dose-escalation clinical trial involving patients with different cancers and they confirmed intratumoral delivery and replication of the adenovirus. *See* Nemunaitis *et al.* at 749, Table 1, and Fig. 3 and 4. In another article authored by Shirakawa *et al.* (Appendix E), mice were treated for osteosarcoma pulmonary metastasis using an intravenously administered adenovirus containing a thymidine kinase gene. Therefore, the Action's contention that intravenous delivery of gene therapy vectors is problematic has been rebutted.

Finally, claims 59-78 are directed to a "method of treating a human cancer patient comprising instilling intratracheally" an Ad-p53 composition. Example 6 directly addresses these claims by showing the tumors in nude mice were treated with Ad-p53 after intratracheal

instillation. Specification at pages 40-41. Additionally, the Action has not provided any evidence that this mode of administration would not work. Thus, claims 59-78 are clearly enabled.

Applicants have addressed the issues raised in the Action. Applicants contend that the claimed invention works as is taught by the specification. Accordingly, claims 22-78 are enabled, and Applicants respectfully request this rejection be withdrawn.

D. Declaration of Deborah R. Wilson Provides Proof Claimed Invention Is Enabled

Applicants submit the declaration of Deborah R. Wilson, the Associate Vice President of Clinical Research at Introgen Therapeutics ("Introgen") as evidence that the rejected claims are enabled (Appendix F). Dr. Wilson's declaration sets forth the numerous clinical trials, involving Introgen's INGN 201 adenovirus-p53 composition, which is disclosed in the specification of the present application, that are underway or have recently been completed or that have been approved. The declaration also sets forth a number of clinical trials that have employed another adenoviral p53 construct, Schering Plough's SCH 58500 adenovirus-p53 construct.

Applicants point to the U.S. Patent and Trademark Office's own training guide, albeit on utility instead of enablement, which states, "[A]s a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility." Because the requirements for utility and enablement are intertwined, Applicants contend that the submission of bountiful clinical trial evidence strongly weighs against a rejection for enablement. The clinical trial evidence shows that adenovirus-p53 is being tested against a number of cancers, including head and neck, non-small cell lung

carcinoma, ovarian, breast, esophageal, lung, glioma, prostate, bladder, and solid tumors from colon cancer, breast cancer, prostate cancer, sarcomas, non-small cell lung carcinomas, and head and neck cancer. This evidence further indicates that administration of Ad-p53 is achieved regionally, intravenously, directly, intraperitoneally, and intravesically. The specification shows intratracheal administration of mice. The Declaration of Deborah R. Wilson confirms the enablement of the claimed invention. Applicants respectfully request the rejection of all the claims for lack of enablement be withdrawn in view of the foregoing reasons.

E. Provisional Obviousness-type Double Patenting Rejection Will Be Addressed

The Action rejects claims 22-97 are provisionally rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-13, 22-26, 28-52, and 56-72 of co-pending Application No. 08/459,713 (INRP:019). Claims 22-97 were also rejected over claims 30-35 in co-pending Application No. 08/626,678 (INRP:005--1). As both of these rejections are provisional, Applicants reiterate that they will submit a terminal disclaimer, if appropriate, once claims in this case are otherwise in condition for allowance and claims in either of the cited applications are deemed allowed.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,

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